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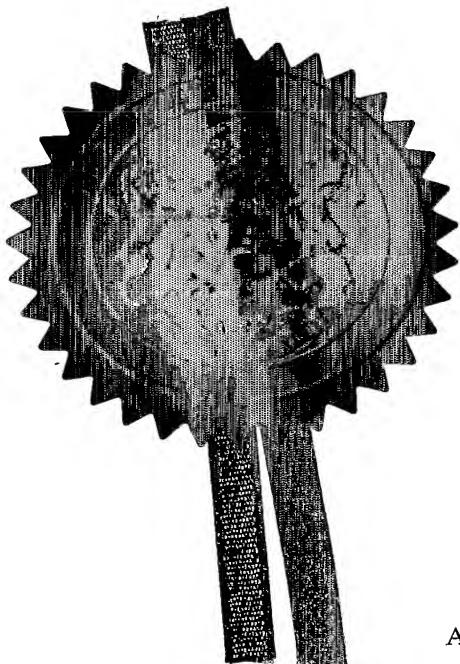
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Manchester  
M60 1QD

5880984005

Paterson Institute for Cancer Research  
Wimslow Road  
Manchester  
M20 4BX

8049769001



## TREATMENT OF CANCER

The present invention relates to the treatment of cancer, more particularly but not exclusively, treatment of cancers that are resistant to platinum based chemotherapeutic agents.

The platinum drugs (e.g. cisplatin and carboplatin, also known as cisplatin and carboplatin respectively) are widely used and clinically active anti-tumour agents. Their activity is based on the ability to cross-link DNA so as to inhibit DNA replication or transcription thus hindering cell proliferation and slowing tumour growth.

One limitation to the activity of the platinum drugs is the development of resistance, resulting in a decrease or loss of anti-tumour activity. The biochemical and pharmacological changes that give rise to resistance to the platinum agents are complex and a number have been described including increased glutathione, altered DNA repair processes, and metallothioneins.<sup>1</sup> One DNA repair process that has been implicated is the loss or reduction of DNA mismatch repair.<sup>2</sup> The development of new therapies that can overcome or circumvent this resistance would have an implication on the treatment in a number of human cancers, including ovarian and lung cancer.

The use of gold-based compounds in cancer chemotherapy has been based upon a series of rationales: analogies between square planar-based Pt(II) and Au(III); analogy to the immunomodulatory effects of Au(I); and complexation of both Au(I) and Au(III) to known anti-tumour agents.<sup>3</sup> The use of Au(I)-based compounds in cancer treatment has focused upon compounds that contain phosphorus, sulfur-based ligand sets that are achiral or chiral, or upon biologically relevant ligands.<sup>4</sup> To-date the use of organometallic gold-containing complexes has centered on the use of Au(III) systems due to their structural and electronic similarities to the known Pt(II)-based systems such as cisplatin and carboplatin.<sup>4,5</sup>

According to a first aspect of the present invention there is provided a pharmaceutical composition for the treatment of cancer comprising an effective amount of a compound having a gold(I) atom covalently bonded to a carbon atom and a pharmaceutically acceptable excipient.

A second aspect of the present invention provides a compound having a gold (I) atom covalently bonded to a carbon atom for use as a chemotherapeutic agent.

A third aspect of the present invention provides the use of a compound having a gold (I) atom covalently bonded to a carbon atom in the preparation of a medicament for the treatment of cancer.

A fourth aspect of the present invention provides a method of treating a cancer in a human or animal patient comprising administering to said patient a therapeutically effective amount of a compound having a gold (I) atom covalently bonded to a carbon atom.

The present invention is based on the observation that compounds comprising a gold(I) atom covalently bonded to a carbon atom exhibit unexpectedly high potency in cell toxicity studies and DNA cross-linking assays which indicate that pharmaceutical compositions comprising such compounds should show efficacy in the treatment of cancer.

It has been observed that compounds forming part of the present invention are much more potent than the platinum drugs across cell lines which are sensitive to the platinum drugs and cell lines which are resistant to the platinum drugs. The present invention therefore provides chemotherapeutic agents which are likely to exhibit significantly improved efficacy in cancer treatment compared to the platinum drugs.

Furthermore, the inventive compounds show especially high potency in cell lines which are cisplatin or carboplatin resistant. The present invention therefore provides chemotherapeutic agents which should be particularly effective in treating cancers which are no longer responsive to treatment with the platinum drugs.

The present invention therefore represents an important step forward in the treatment of cancer, especially in cases where the tumour cells have developed a resistance to the platinum drugs.

Preferably the chemotherapeutic agent employed in the invention (i.e. the compound having a gold (I) atom covalently bonded to a carbon atom) incorporates a substituted or unsubstituted aromatic group. Furthermore, the carbon atom covalently bonded to said gold(I) atom may be part of said aromatic group which itself may be a substituted or unsubstituted phenyl group.

The chemotherapeutic agent is preferably comprised of a compound comprising a first gold(I) atom covalently bonded to a first carbon atom and a second gold(I) atom covalently bonded to a

second carbon atom. It is preferred that the first carbon atom is part of a substituted or unsubstituted aromatic group. The aromatic group may be a substituted or unsubstituted phenyl group. The second carbon atom may be part of a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group. Preferably the second carbon atom is part of an aromatic group, preferably a substituted or unsubstituted phenyl group.

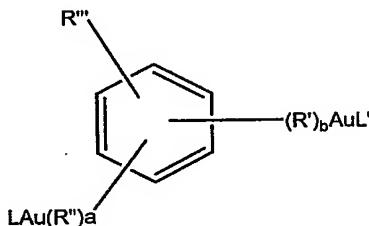
In further preferred embodiments of the invention the chemotherapeutic agent incorporates a ligand bonded to the or at least one of the said gold(I) atoms, said ligand being selected from the group consisting of  $PR_3$ ,  $P(OR)_3$ ,  $CNR$ ,  $NCR$ ,  $PR_n(CH_2OR^\ddagger)_{3-n}$ ,  $N_4C_6H_{12}$ ,  $[N_4C_6H_{12}-N-CH_3]^+$ ,  $PN_3C_6H_{12}$ , and  $P[N_3C_6H_{12}-N-CH_3]^+$ , where R is a substituted or unsubstituted hydrocarbon moiety and  $R^\ddagger$  is selected from the group consisting of H, Me,  $SO_2^-$ ,  $PO_3^-$ , alkyl and aryl, and each  $R^\ddagger$  in any one ligand is the same or different. Preferably R is a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group and each R in any one ligand is the same or different. Moreover, R may be selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl groups. In a particularly preferred embodiment of the invention, the ligand is  $PPh_3$ .

The chemotherapeutic agent may be administered to a patient as an adjuvant to surgery or radiotherapy. Additionally or alternatively, the agent may be administered to the patient in combination with at least one further chemotherapeutic agent.

The inventive compositions may be administered by any route as conventionally employed for chemotherapeutic agents. Thus the agent may be given intravenously or orally in tablet form. The compound may be given by intramuscular, subcutaneous, intrathecal or, particularly in the case of treating ovarian cancer, intraperitoneal injection.

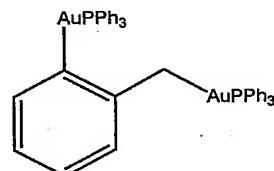
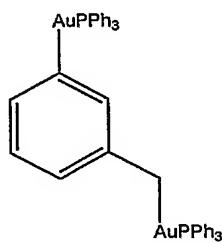
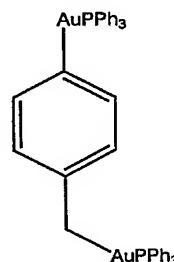
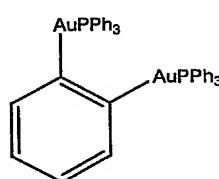
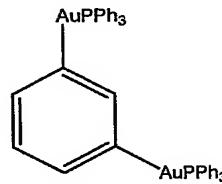
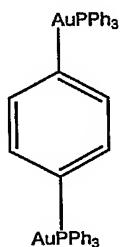
In the case of intravenous administration, the chemotherapeutic agents may be given to the patient up to twelve times with a gap of up to approximately four weeks between each treatment. In this case the intravenous administration may be injection into a vein over a relatively short period of time, e.g. a few minutes, or through a drip by intravenous infusion over longer periods of time, such as between about 30 minutes and a few hours. Alternatively, the agents may be administered intravenously by continuous infusion (also known as protracted venous infusion or ambulant infusion) over longer periods of time, e.g. from a few days up to a number of weeks or months, by use of an infusion pump via a central line.

A first class of preferred compounds forming part of the present invention is represented by formula 1:

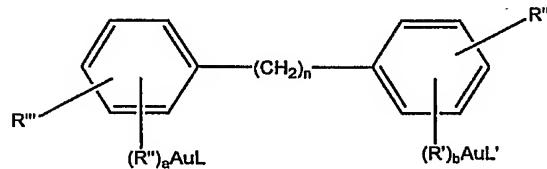


Formula 1

Where: L and L' are ligands; R' and R'' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; and b is 0 or 1. The substitution pattern on the aromatic ring of the gold moieties may be ortho, meta or para.  $R'''$  may be H,  $SO_3^-$ ,  $PO_4^{2-}$ ,  $CO_2H$ , OH,  $(CH_2)_nCH_3$ ,  $O(CH_2)_nCH_3$ ,  $S(CH_2)_nCH_3$ , or  $NR'''C(O)(R''')$  where  $R'''$  and  $R''''$  are  $(CH_2)_nCH_3$ . n is 0 to 6. Preferred examples of this class of compound are selected from the group consisting of:

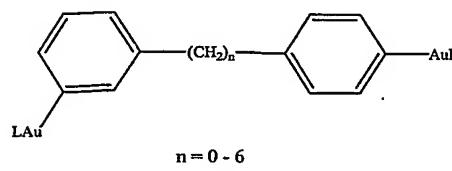
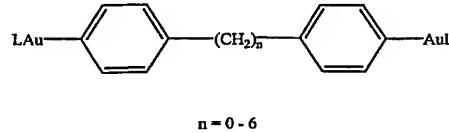
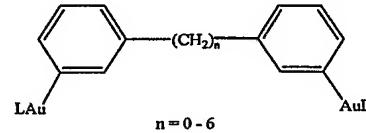
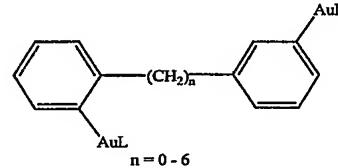
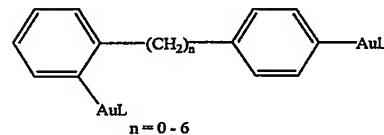
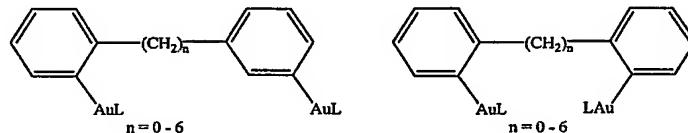


A second class of compounds forming part of the present invention is represented by formula 2:

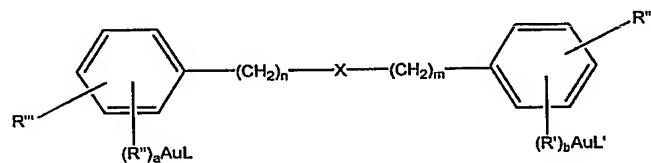


Formula 2

where: L and L' are ligands; R' and R' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; R''' may be H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R''' and R'''' are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6. Preferred examples of this class of compound are selected from the group consisting of:

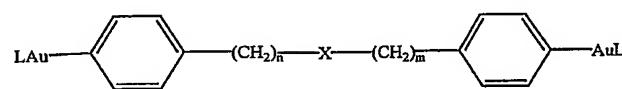
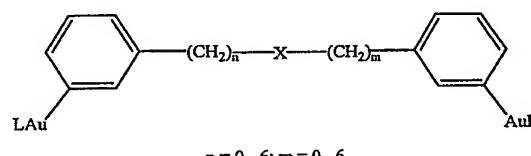
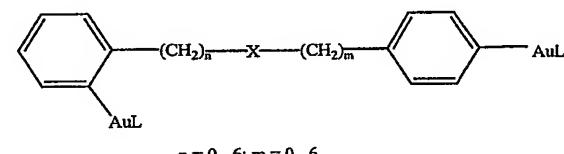
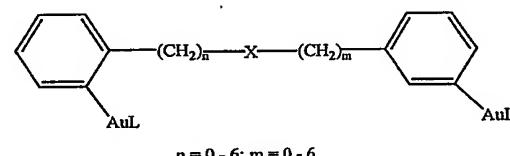
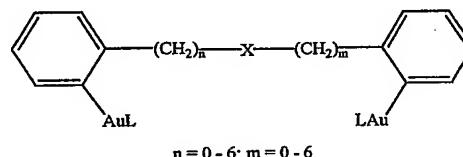


A third class of compounds forming part of the present invention is represented by formula 3:

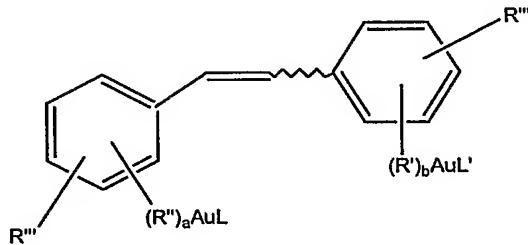


Formula 3

where: L and L' are ligands; R' and R'' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; and X is a linking group. X may be selected from the group consisting of: O, S, PR or NR in which R is a substituted or unsubstituted hydrocarbon moiety. R''' may be H, SO<sub>3</sub><sup>-</sup>, PO<sub>4</sub><sup>2-</sup>, CO<sub>2</sub>H, OH, (CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, S(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, or NR'''C(O)(R''') where R''' and R'''' are (CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>. n is 0 to 6 and m is 0 to 6. Preferred examples of this class of compound are selected from the group consisting of:

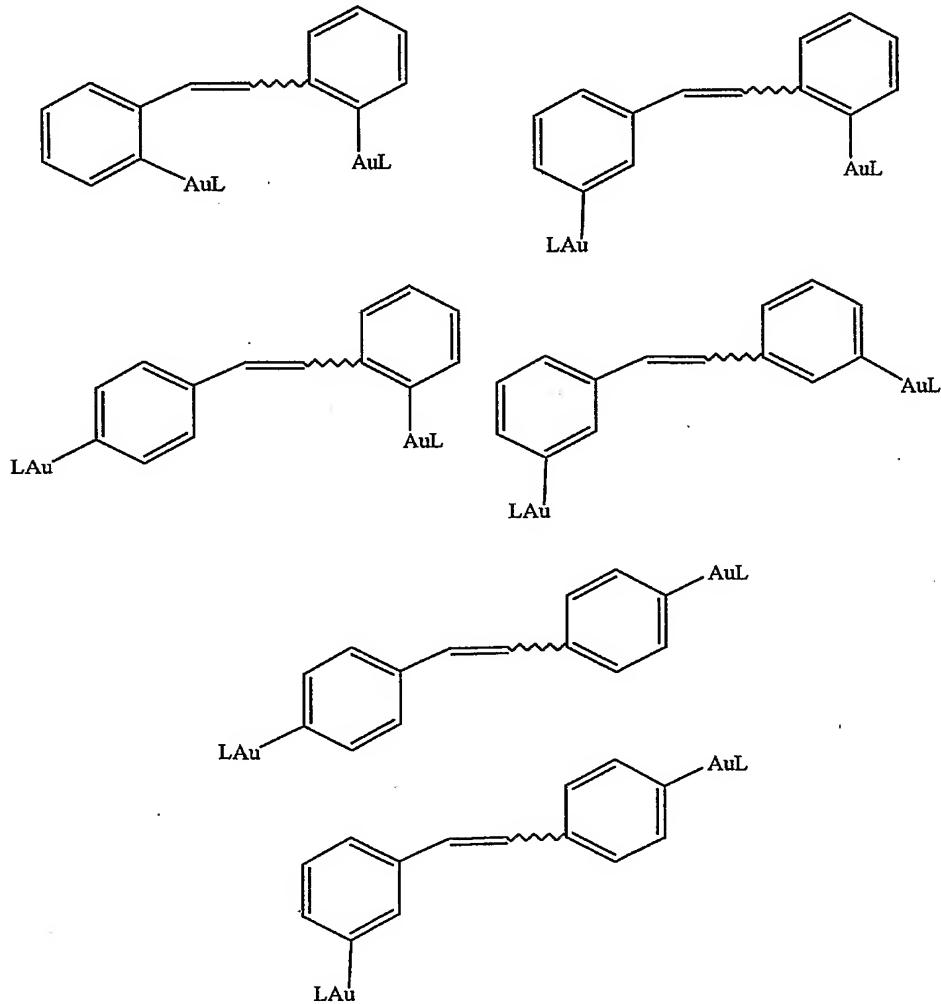


A fourth class of compounds forming part of the present invention is represented by formula 4:

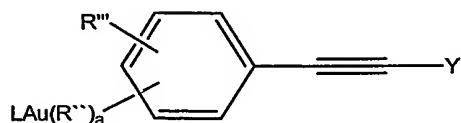


Formula 4

— where: L and L' are ligands; R' and R'' are substituted-or-unsubstituted-divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; R''' may be H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R'''' and R''''' are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6. Preferred examples of this class of compound are selected from the group consisting of:

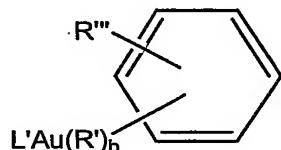


A fifth class of compounds forming part of the present invention is represented by formula 5:



Formula 5

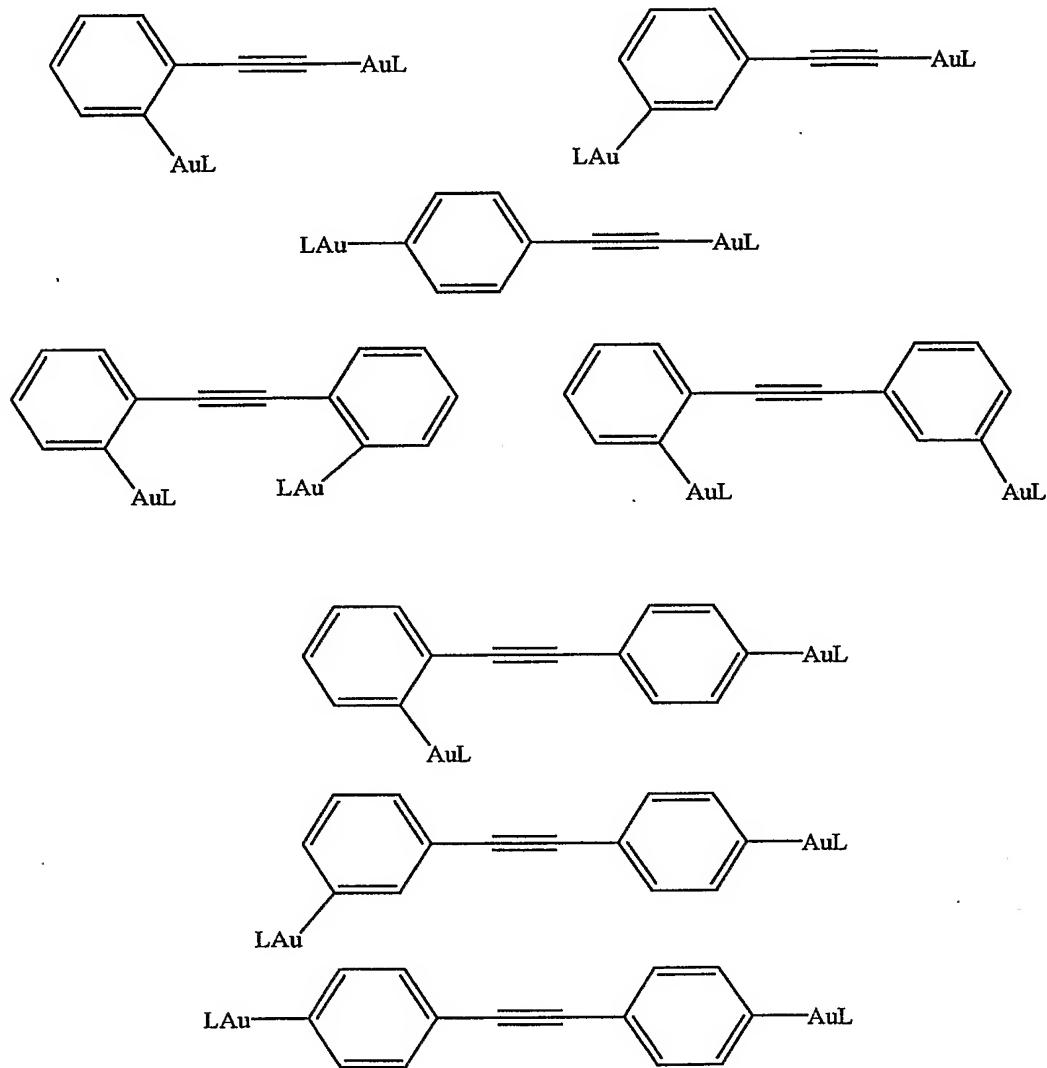
where: Y is any chemical group; L is a ligand; R'' is a substituted or unsubstituted divalent hydrocarbon moiety; a is 0 or 1; R''' may be H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where  $\text{R}''''$  and  $\text{R}'''''$  are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6. In preferred embodiments of this class of compounds Y is selected from the group consisting of:  $(\text{R}')_b\text{AuL}'$  and;



where: L' is a ligand; R' is a substituted or unsubstituted divalent hydrocarbon moiety; b is 0 or 1; R''' may be H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where  $\text{R}''''$  and  $\text{R}'''''$  are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6.

In preferred embodiments of the invention L and L' are the same. Furthermore, preferably R' and R'' are the same.

Preferred examples of this class of compound are selected from the group consisting of:



In formulae 1-5, L and L' may be the same or different. L and/or L' may be selected from the group consisting of  $PR_3$ ,  $P(OR)_3$ , CNR, NCR,  $PR_n(CH_2OR^\ddagger)_{3-n}$ ,  $N_4C_6H_{12}$  (hexamethylenetetraamine),  $[N_4C_6H_{12}-N-CH_3]^+$ ,  $PN_3C_6H_{12}$ , and  $P[N_3C_6H_{12}-N-CH_3]^+$ , where R is any desirable substituted or unsubstituted hydrocarbon moiety e.g. a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group. Thus R may be selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl groups. It is particularly preferred that each R group in  $PR_3$  is phenyl and that the ligand is  $PPh_3$ . Moreover, R' and R'' may each be independently selected from the group consisting of methylene, ethylene, propylene, butylene and phenylene groups.  $R^\ddagger$  is selected from the group consisting of H,  $SO_2^-$ ,  $PO_3^-$ , alkyl (in particular methyl) and aryl, and each  $R^\ddagger$  in any one ligand may be the same or different.

The invention is illustrated with reference to the following non-limiting Example and accompanying drawings, in which:

Figure 1 is a graphical representation of DNA cross-linking in parental and resistant cell lines following treatment with cisplatin;

Figure 2 is a graphical representation of DNA cross-linking in parental and resistant cell lines following treatment with carboplatin;

Figure 3 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound A;

Figure 4 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound B;

Figure 5 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound C;

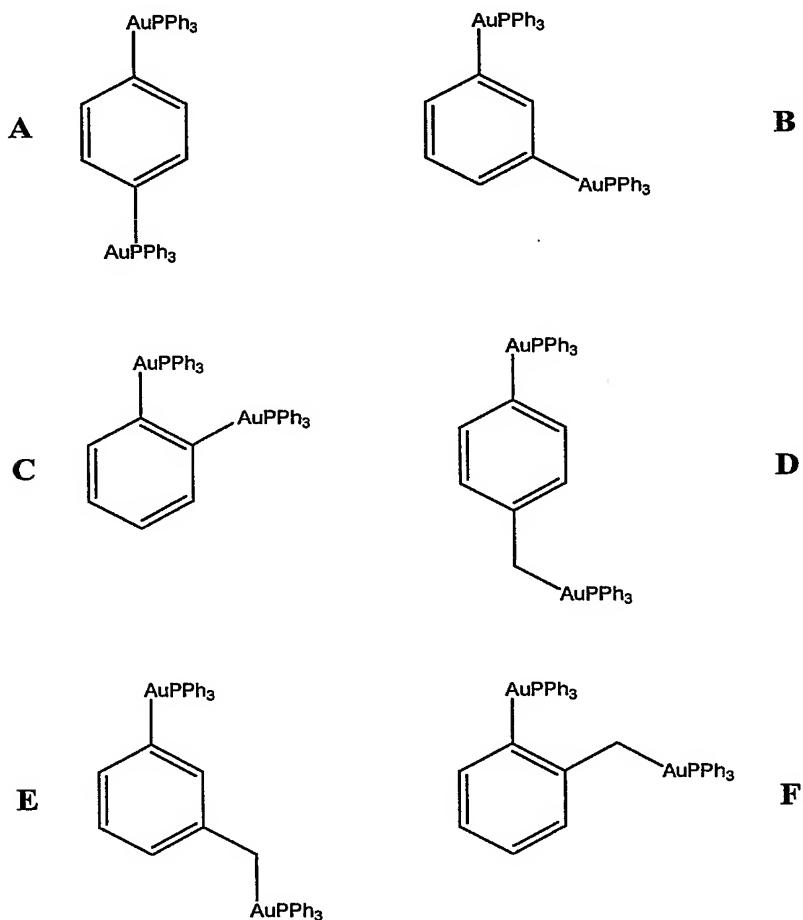
Figure 6 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound D;

Figure 7 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound E; and

Figure 8 is a graphical representation of DNA cross-linking in parental and platinum-resistant cell lines following treatment with compound F.

EXAMPLE

A comparison of the chemotherapeutic activity of compounds **A** – **F** (below) and that of cisplatin and carboplatin was made using a series of paired cell lines that are known to be either sensitive or have acquired resistance to the clinically useful agents cisplatin and carboplatin. For details of the synthesis of compound **A** see Appendix A.



The sensitivities of the cell lines to cisplatin, carboplatin, and compounds **A** – **F** were determined using a growth inhibition assay which was a modified version of the MTT method (modified version of MTT method described in Appendix B).

The following is a brief description of the eleven different cell lines used in the growth inhibition assay:

- The A2780 cell line (**1** in figures 1-9) is a human ovarian cell line which is sensitive to cisplatin and carboplatin. The A2780cis (**2**) and A2780carb (**3**) cell lines are modified versions of the A2780 cell line which exhibit cisplatin and carboplatin resistance respectively.
- Cell lines mcp1 (**4**) and mcp8 (**5**) are platinum-resistant A2780 sublines which are mismatch repair deficient.
- The cor123 (**6**) is a non small cell lung cancer cell line which is sensitive to the platinum drugs. The cor123/cpr (**7**) cell line is a modified version of the cor123 cell line which has been modified to be resistant to cisplatin and carboplatin.
- The ccu24 (**8**) cell line is an epithelial ovarian cancer cell line, developed at the Christie Hospital from a tumour biopsy, and the ccu24/cpr (**9**) cell line is a modified version of this cell line which is cisplatin and carboplatin resistant.
- L1210 (**10**) is a murine leukemia cell line and L1210/M1140 (**11**) is its platinum drug resistant subline.

Table 1 illustrates the results of a first series of assays which were carried out to investigate the activity of each of the six inventive compounds (**A – F**) and cisplatin. Table 2 illustrates the results of a further series of assays carried out on compounds **A – F**, and carboplatinum.

Drug	Cell line										
	A2780 -S	A2780 cis	A2780 carb	corl23	corl23 /cpr	ccu24	ccu24/ cpr	L1210	L1210/M	mcp1	mcp8
A	13.4	0.2	0.6	19.3	1.5	25.3	3.6	38.3	6.4	0.5	0.6
B	9.8	0.2	0.4	12.6	1.2	18.7	2.1	26.6	4.1	0.4	0.4
C	12.8	0.3	0.5	14.4	1.4	20.2	3.3	42.7	5.2	0.5	0.5
D	32.4	7.3	10.3	22.3	15.7	36.4	12.5	48.7	17.4	8.4	6.8
E	8.9	0.4	0.6	17.7	1.4	10.2	2.4	32.5	5.3	0.9	0.9
F	20.4	5.4	7.3	28.2	11.4	22.1	9.5	28.1	11.4	6.3	5.3
Cisplatin	1320	30460	27640	3430	26650	4320	24850	12140	44860	19860	24450

Table 1: IC<sub>50</sub> (nM) of compounds tested.

Drug	Cell line										
	A2780 -S	A2780 cis	A2780 carb	corl23	corl23 /cpr	ccu24	ccu24/ cpr	L1210	L1210 /M1140	A2780/ mcp1	A2780/ mcp8
A	16.5	0.5	0.9	22.2	4.5	28.3	6.4	41.6	9.2	3.5	4.6
B	12.1	0.6	0.7	15.8	4.3	21.8	5.1	29.6	7.2	3.5	5.4
C	15.2	0.6	0.8	17.6	4.4	23.2	6.3	45.8	8.4	3.5	4.6
D	36.6	10.2	13.5	25.4	19.7	39.5	15.6	50.3	20.6	19.5	14.8
E	11.2	0.7	0.9	21.1	4.4	13.5	5.4	35.6	8.5	3.9	4.7
F	24.3	8.3	10.4	31.1	14.6	26.4	12.2	31.2	14.4	10.4	11.4
Carbo platin	1590	34580	32150	5350	29820	5820	27190	15320	47780	24780	26750

Table 2: IC<sub>50</sub> values (nM) of compounds tested.

The results shown in Table 2 illustrate the reproducibility of the data shown in Table 1.

The data on the effects of compounds A - F on the eleven cell lines can be summarized as follows:

- 1) Compounds A - F are considerably more potent than the platinum drugs (nM compared to  $\mu$ M); and
- 2) The inventive compounds A - F are more active in the platinum-resistant cell lines than in the parental cell lines. Taking compound A as an example:
  - a) The A2780cis cell line ( $IC_{50}$  0.2 nM) is over sixty-times more sensitive to compound A than the parental (sensitive) A2780-S line ( $IC_{50}$  13.4 nM); and
  - b) The A2780carb cell line ( $IC_{50}$  0.6 nM) is over twenty-times more sensitive to compound A than the parental A2780-S line ( $IC_{50}$  13.4 nM).

This collateral sensitivity is seen in both mouse and human tumour cell lines.

Preliminary studies have been carried out to investigate the mechanism underlying this increased sensitivity. These studies were carried out using the Comet assay (described in Appendix C), which measures damage to DNA. The results are shown in Figures 1 (cisplatin), 2 (carboplatin) and 3 to 8 (compounds A - F).

It can be seen from Figures 1 and 2 that both cisplatin and carboplatin cause extensive DNA cross-linking in the parental (platinum-sensitive) A2780, L1210, and cor123 cell lines, whereas much less cross-linking is seen in the platinum-resistant cell lines. This is in agreement with the hypothesis that DNA is the target for the platinum drugs and that resistance arises due to a reduction of DNA damage in the resistant cells. This can arise by a number of mechanisms including DNA repair, increased deactivation of drug, or decreased drug uptake.

In contrast, it can be seen from Figures 3 to 8 that compounds A - F cause more DNA damage in the platinum-resistant cell lines than in the parental (platinum-sensitive) cell lines.

Table 3 illustrates the results of the following calculation using the DNA cross-linking results obtained in the Comet assays:

DNA cross - linking in the parental (sensitive) cell line  
DNA cross - linking in the platinum drug resistant cell line

Drug	Cell line						
	A2780cis	A2780carb	cor123	ccu24	L1210	A2780mcp1	A2780/mcp8
A	0.50	0.53	0.56	0.40	0.69	0.59	0.60
B	0.36	0.37	0.38	0.39	0.47	0.40	0.39
C	0.36	0.36	0.38	0.37	0.71	0.38	0.41
D	0.54	0.63	0.62	0.47	0.63	0.48	0.50
E	0.39	0.40	0.43	0.46	0.40	0.41	0.48
F	0.52	0.61	0.62	0.60	0.53	0.54	0.56
cisplatin	5.65	8.08	5.72	4.65	3.37	5.40	5.70
Au (III)	0.67	0.71	0.83	0.78	0.54	0.72	0.69
Au (I)	1.00	1.33	0.75	1.00	1.33	1.33	1.33

Table 3: Summary of DNA crosslinking (Comet) experiments. Au(I) and Au(III) are the values for the uncomplexed metal ions.

The results for cisplatin show the expected trend of increased activity (i.e. a ratio greater than unity) in the parental cell lines compared to the platinum-resistant cell lines. Each of the inventive compounds (A – F) possess ratios of significantly below 1.00 for all of the resistant cell lines, thus confirming the above observation that compounds A – F cause more DNA cross-linking in the platinum-resistant cell lines than in the parental (platinum-sensitive) cell lines.

Compounds A – F therefore show enhanced cell killing in platinum-resistant cell lines *in vitro*, which is likely to be due to increased DNA damage in the platinum-resistant cell lines. The exact mechanism that underlies this has not yet been fully elucidated. However activity is seen in the platinum resistant miss-match repair deficient mcp1<sup>6</sup> and mcp8 cell lines. It is therefore proposed

that the inventive compounds are likely to show enhanced activity in tumours that are mis-match repair deficient.

Compounds **A – F** are simple metal compounds and do not contain platinum. The ability of the inventive compounds to selectively kill platinum-resistant cells may have important clinical implications as resistance to platinum drugs is cited as a cause of the failure of therapy in a number of cancers including ovarian and lung.

## APPENDIX A

### Synthesis of the Compounds

All solvents were dried and distilled under an N<sub>2</sub> atmosphere prior to use. All chemicals were purchased from commercial sources apart from [ClAu(SC<sub>4</sub>H<sub>8</sub>)] which was prepared by the literature method.<sup>14</sup>

#### Preparation of 1,4-bis-(triphenylphosphinogold(I))benzene (A)

To 1,4-dibromobenzene (0.074 g, 0.31 mmol) dissolved in ether (20 mL) at -78° was added tertiary butyl lithium (0.75 mL, 1.25 mmol) and the reaction mixture allowed to stir for 30 min. To this mixture was added thiophene (5 mL) and [ClAu(SC<sub>4</sub>H<sub>8</sub>)] (0.200 g, 0.62 mmol) and the reaction stirred for 1.5 hours. Triphenylphosphine (0.083 g, 0.32 mmol) was then added and the solution stirred for another 1.5 hours before warming to room temperature and stirring for another 30 min. The diethyl ether was then removed under reduced pressure, the crude material extracted into dichloromethane and filtered to remove lithium salts. The compound was then recrystallised from hot ether; yield 0.286 g, 93 %. mp 139° decomp. NMR: <sup>1</sup>H: 7.70 – 7.49 ppm aryl-H; <sup>31</sup>P{<sup>1</sup>H}: 44.8 ppm; <sup>13</sup>C{<sup>1</sup>H}: 168.0, 139.7, 133.3, 130.2, 128.1, 131.0 ppm; Microanalysis: Found C = 50.2; H = 3.9; P = 6.0; Calc: C = 50.7; H = 3.4; P = 6.2.

In a similar manner the compounds [1,4-bis-(LAu)C<sub>6</sub>H<sub>4</sub>] can be prepared where L is any desirable ligand, for example, CNBu<sup>t</sup>, PEt<sub>3</sub>, P(OMe)<sub>3</sub> or NCMe.

This experimental procedure can be extended to other polyaromatic systems. An example of which is 4,4'-bis-(triphenylphosphinogold(I))biphenyl.

#### Preparation of 4,4'-bis-(triphenylphosphinogold(I))biphenyl.

##### Method 1 – Using [ClAu(SC<sub>4</sub>H<sub>8</sub>)]

To 4,4'-dibromobiphenyl (0.096 g, 0.31 mmol) dissolved in ether (20 mL) at -78° was added tertiary butyl lithium (0.75 mL, 1.25 mmol) and the reaction mixture allowed to stir for 30 min. To this mixture was added thiophene (5mL) and [ClAu(SC<sub>4</sub>H<sub>8</sub>)] (0.200g, 0.62 mmol) and the

reaction stirred for 1.5 hours. Triphenylphosphine (0.083 g, 0.62 mmol) was then added and the solution stirred for another 1.5 hours before warming to room temperature and stirring for another 30 min. The diethyl ether was then removed under reduced pressure, the crude material extracted into dichloromethane and filtered to remove lithium salts. The compound was then recrystallised from hot ether; yield 0.275 g, 83 %. mp 138° decomp. NMR:  $^1\text{H}$ : 7.70 – 7.47 ppm aryl-H;  $^{31}\text{P}\{\text{H}\}$ : 44.9 ppm ;  $^{13}\text{C}\{\text{H}\}$  : 170.5, 139.9, 134.8, 131.6, 131.5, 129.5, 126.4 ppm; Microanalysis: Found: C = 53.8, H = 3.6, P = 5.8; Calc: C = 53.2; H = 3.6; P = 6.1.

In a similar manner the compounds [1,4-bis-(LAu)C<sub>6</sub>H<sub>4</sub>] can be prepared where L is any desirable ligand, for example, CNBu<sup>t</sup>, PEt<sub>3</sub>, P(OMe)<sub>3</sub> or NCMe.

#### Method 2 – Using [ClAu(AsPh<sub>3</sub>)]

To 4,4'-dibromobiphenyl (0.096 g, 0.31 mmol) dissolved in ether (20 mL) at -78° was added tertiary butyl lithium (0.75 mL, 1.25 mmol) and the reaction mixture allowed to stir for 30 min. To this mixture was added thiophene (5mL) and [ClAu(AsPh<sub>3</sub>)] (0.128g, 0.62 mmol)<sup>15</sup> and the reaction stirred for 1.5 hours. Triphenylphosphine (0.083 g, 0.62 mmol) was then added and the solution stirred for another 1.5 hours before warming to room temperature and stirring for another 30 min. The diethyl ether was then removed under reduced pressure, the crude material extracted into dichloromethane and filtered to remove lithium salts. The compound was then recrystallised from hot ether; yield 0.265 g, 80%. mp 138° decomp. NMR:  $^1\text{H}$ : 7.70 – 7.47 ppm aryl-H;  $^{31}\text{P}\{\text{H}\}$ : 44.9 ppm ;  $^{13}\text{C}\{\text{H}\}$  : 170.5, 139.9, 134.8, 131.6, 131.5, 129.5, 126.4 ppm; Microanalysis: Found: C = 53.6, H = 3.5, P = 6.1; Calc: C = 53.2; H = 3.6; P = 6.1.

In a similar manner the compounds [1,4-bis-(LAu)C<sub>6</sub>H<sub>4</sub>] can be prepared where L is any desirable ligand, for example, CNBu<sup>t</sup>, PEt<sub>3</sub>, P(OMe)<sub>3</sub> or NCMe.

4,4'-bis-(triphenylphosphinogold(I))biphenyl has also been characterised by a single crystal X-ray diffraction study:

Crystal form: Monoclinic

Space Group P21/c

$a = 18.6224(2)$  Å

$b = 10.27190(10)$  Å

$c = 24.0682(3)$  Å

$\beta = 102.634^\circ$

$Z = 4$

$T = 150$  K

$R_1 = 4.05.$

**APPENDIX B****Growth Inhibition Assay**

The cell toxicity studies were performed using a modification of the method MTT.<sup>7</sup> The principle of the assay is to assess the growth inhibitory effect of a drug at various doses over a five-day time course. This assay was performed in 96-well microtitre plates. Cells were seeded at densities of 400-1,000 cells per well, depending on the doubling time of the cell line. All cell dilutions were performed in growth medium containing 10% FCS (foetal calf serum).

Compounds under investigation were dissolved in DMSO (dimethylsulphoxide). Serial dilutions of compound were made into the cell suspension, ensuring that the proportion of DMSO remained below 0.5%. 200 $\mu$ l of cells and drug mix was added to the 96-well plates in triplicate. The plates were incubated for five days at 5% CO<sub>2</sub> and 37°C. After this time, the plates were removed from the incubator and 50 $\mu$ l of a 3mg/ml solution of MTT [3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide] was added to each well and incubated in the same conditions for another 3 hours. The medium from each well was aspirated and the formazan crystals were solubilised in 200 $\mu$ l of DMSO. The plates were read using a Multiskan platereader at 540nm and 690nm. Growth inhibition curves were constructed using mean and standard deviation of the triplicate absorbance values and from these curves the IC<sub>50</sub> values were calculated.

## APPENDIX C

### Comet Assay

DNA damage was measured by the single cell gel electrophoresis (SCGE) assay or "Comet assay", originally developed by Ostling and Johnson<sup>8</sup>. This is a method for determining the extent of DNA damage and repair capacity within individual cells.<sup>9-11</sup> It has previously been shown that this technique can be used to investigate the mechanism of action of different DNA damaging agents.<sup>12</sup>

Cells were trypsinised, suspended in 0.5ml of ice cold fresh medium and transferred into plastic 24-well dishes prior to embedding in agarose. For the cross-linking studies treated and control samples were chilled on ice (to prevent any repair of DNA damage) and irradiated to a dose of 20Gy in a Caesium-137 source (0.4Gy/min). Control, (unirradiated, non-drug treated cells) were maintained on ice in the same manner as treated samples.

Glass microscope slides, frosted at one end, were pre-coated with 1% normal agarose in distilled water. These slides were allowed to air dry overnight prior to use. A 1% low melting point agarose (LMP) mixture in PBS was melted and held at 45°C. 1ml of LMP was then added to 0.5ml of cell suspension on ice and the resultant mixture was pipetted onto a pre-coated glass microscope slide and allowed to set for 1-2 minutes before being transferred to an ice tray. The slides were immersed in ice cold lysis solution (100mM EDTA, 10mM Tris-HCl, 1% Triton X100, 1% DMSO, 2.5M NaCl) for 1hr, and washed three times by immersion in fresh double distilled water for 15 minutes.

Slides were then placed onto a flat bed electrophoresis tank and covered (5-6mm) with alkali unwinding solution (50mM NaOH, 1mM EDTA buffered to pH 12.5) and left under subdued lighting for 45 minutes to allow the DNA to unwind before being subjected to electrophoresis at 0.6V/cm for 25 minutes. Each slide was rinsed with 2 x 1ml of 0.4M Tris-HCl, pH 8.0 and allowed to dry in air. The dried slides were then rehydrated for 20 minutes with double distilled water, 2 x 1ml of propidium iodide solution (2.5µg/ml) was added and staining was allowed to proceed for 15 minutes. Slides were then immersed in 1 litre of double distilled water for 1 hour to reduce excess background staining. The slides were cover slipped and then examined at 250 x magnification under an epifluorescent microscope (Zeiss-Jenamed) using green light from a 50

watt mercury source with a 580nm reflector and a 590nm barrier filter set. Images were captured using an attached Sony HAD-1 interline CCD camera and Komet software analysis package (Kinetic Imaging). Twenty-five images from each of two duplicate slides were captured and analysed and the individual "comet moments" as defined by Olive *et al*<sup>13</sup>, were calculated. The total fluorescence of the image represents the amount of DNA present and the length of the image, measured in pixels, represents the length of migration of the DNA. The head and tail areas of the image were identified and the intensity of each was determined. The tail moment is calculated by multiplying the fraction of DNA present in the tail by half the length of the tail.

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REFERENCES

1. Hrubisko, M., McGown, A.T., Fox, B.W. "The role of metallothionein, glutathione, glutathione S-transferases and DNA repair in resistance to platinum drugs in a series of L1210 cell lines made resistant to platinum agents." *Biochemical Pharmacology*, 1993, **45**, 253-256.
2. Fink, D., Aebi, S., Howell, S.B. "The role of DNA mismatch repair in drug resistance." *Clinical Cancer Research*, 1998, **4**, 1-6.
3. *Chemical Reviews*, 1999, **9**, 2589-2600.
4. *Critical Reviews in Oncology /Hematology*, 2002, **42**, 225-248.
5. *Expert Reviews in Anticancer Therapy*, 2002, **2**, 347-346.
6. Colella G; Marchini S; D'Incalci M. "Mismatch repair is associated with resistance to DNA minor groove alkylating agents." *British Journal of Cancer*, 1999, **80** (3-4), 338-343.
7. Alley, M.C., Scudiero, D.A., Monks, A., Hursey, M.L., Czerwinski, M.J., Fine, D.L., Abbott, B.J., Mayo, J.G., Shoemaker, R.H., Boyd, M.R. "Feasibility of drug screening with panels of human tumor cell lines using a microculture tetrazolium assay." *Cancer research*, 1988, **48**, 589-601.
8. Ostling, O. and Johnson, J. "Microelectrophoretic studies of radiation induced DNA damage in individual mammalian cells." *Biochemical and Biophysical Research Communications*, 1984, **123**, 29-298.
9. McKelvey-Martin, V.J., Green, M.H., Schmezer, P., Pool-Zobel, B.L., De Meo, M.P. and Collins, A. "The single cell gel electrophoresis assay (comet assay): a European review." *Mutatation Research*, 1993, **288**, 47-63.

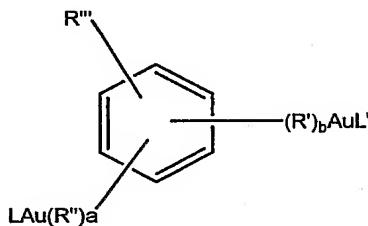
10. Collins, A.R., Fleming, I.M. and Gedik, C.M.. "In vitro repair of oxidative and ultraviolet-induced DNA damage in supercoiled nucleoid DNA by human cell extract." *Biochimica et Biophysica Acta*, 1994, **1219**, 724-727.
11. Olive, P.L. and Banath, J.P. "Sizing highly fragmented DNA in individual apoptotic cells using the comet assay and a DNA crosslinking agent." *Experimental Cell Research*, 1995, **221**, 19-26.
12. Ward, T.H., Butler, J., Shahbakhti, H. and Richards, J.T. (1997). "Comet assay studies on the activation of two diaziridinylbenzoquinones in K562 cells." *Biochemical Pharmacology*, 1997, **53**, 1115-1121.
13. Olive, P.L, Banath, J.P. and Durand, R.E. "Heterogeneity in radiation-induced DNA damage and repair in tumor and normal cells measured using the "comet" assay." *Radiation Research*, 1990, **122**, 86-94.
14. R. Uson, A. Laguna, M. Laguna, *Inorganic Synthesis*, 1989, **26**, 85 – 91.
15. *J. Organomet. Chem.*, 2002, **648**, 1-7.

CLAIMS

1. A pharmaceutical composition for the treatment of cancer comprising an effective amount of a compound having a gold(I) atom covalently bonded to a carbon atom and a pharmaceutically acceptable excipient.
2. A pharmaceutical composition in accordance with claim 1, wherein said compound comprises a substituted or unsubstituted aromatic group.
3. A pharmaceutical composition in accordance with claim 2, wherein said carbon atom is part of said aromatic group.
4. A pharmaceutical composition in accordance with claim 2 or 3, wherein said aromatic group is a substituted or unsubstituted phenyl group.
5. A pharmaceutical composition in accordance with any one of claims 1 to 4, wherein said compound comprises a first gold(I) atom covalently bonded to a first carbon atom and a second gold(I) atom covalently bonded to a second carbon atom.
6. A pharmaceutical composition in accordance with claim 5, wherein the first carbon atom is part of a substituted or unsubstituted aromatic group.
7. A pharmaceutical composition in accordance with claim 6, wherein the first carbon atom is part of a substituted or unsubstituted phenyl group.
8. A pharmaceutical composition in accordance with claim 6 or 7, wherein the second carbon atom is part of a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group.
9. A pharmaceutical composition in accordance with claim 8, wherein the second carbon atom is part of a substituted or unsubstituted phenyl group.
10. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound comprises a ligand bonded to the or at least one of said gold(I) atoms, said

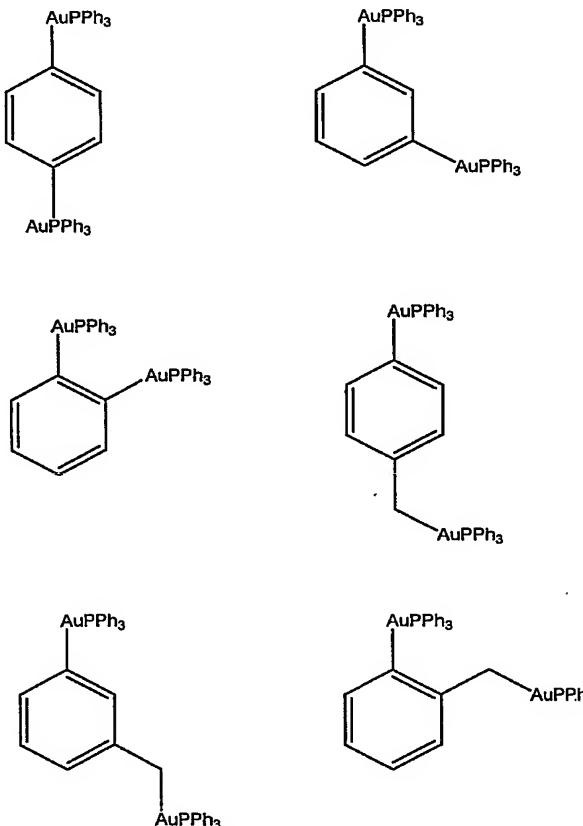
ligand being selected from the group consisting of  $\text{PR}_3$ ,  $\text{P}(\text{OR})_3$ ,  $\text{CNR}$ ,  $\text{NCR}$ ,  $\text{PR}_n(\text{CH}_2\text{OR}^\ddagger)_{3-n}$ ,  $\text{N}_4\text{C}_6\text{H}_{12}$ ,  $[\text{N}_4\text{C}_6\text{H}_{12}-\text{N}-\text{CH}_3]^+$ ,  $\text{PN}_3\text{C}_6\text{H}_{12}$ , and  $\text{P}[\text{N}_3\text{C}_6\text{H}_{12}-\text{N}-\text{CH}_3]^+$ , where R is a substituted or unsubstituted hydrocarbon moiety and  $\text{R}^\ddagger$  is selected from the group consisting of H, Me,  $\text{SO}_2^-$ ,  $\text{PO}_3^-$ , alkyl and aryl, and each  $\text{R}^\ddagger$  in any one ligand is the same or different.

11. A pharmaceutical composition in accordance with claim 10, wherein R is a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group and each R in any one ligand is the same or different.
12. A pharmaceutical composition in accordance with claim 10 or 11, wherein R is selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl groups.
13. A pharmaceutical composition in accordance with claim 10, 11 or 12, wherein the ligand is  $\text{PPh}_3$ .
14. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound has the formula:

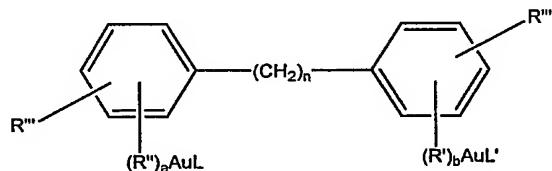


where: L and L' are ligands; R' and R'' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; R''' is H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where  $\text{R}''''$  and  $\text{R}'''''$  are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6.

15. A pharmaceutical composition in accordance with claim 14, wherein said compound has a formula selected from the group consisting of:

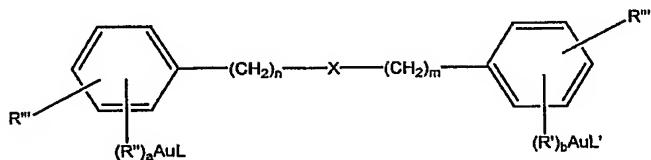


16. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound has the formula:



where:  $\text{L}$  and  $\text{L}'$  are ligands;  $\text{R}'$  and  $\text{R}''$  are substituted or unsubstituted divalent hydrocarbon moieties;  $\text{a}$  is 0 or 1;  $\text{b}$  is 0 or 1;  $\text{R}'''$  is  $\text{H}$ ,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ ,  $\text{OH}$ ,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where  $\text{R}''''$  and  $\text{R}'''''$  are  $(\text{CH}_2)_n\text{CH}_3$ , and  $n$  is 0 to 6.

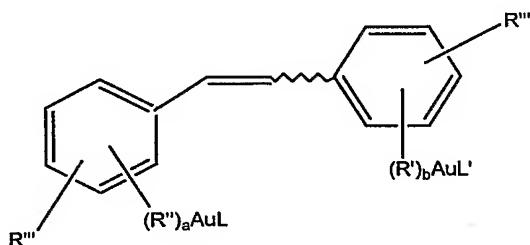
17. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound has the formula:



where: L and L' are ligands; R' and R'' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; R''' is H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R'''' and R''''' are  $(\text{CH}_2)_n\text{CH}_3$ ; n is 0 to 6; m is 0 to 6; and X is a linking group.

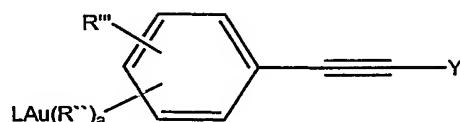
18. A pharmaceutical composition in accordance with claim 17, wherein X is selected from the group consisting of: O, S, PR or NR in which R is a substituted or unsubstituted hydrocarbon moiety.

19. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound has the formula:



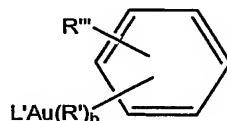
where: L and L' are ligands; R' and R'' are substituted or unsubstituted divalent hydrocarbon moieties; a is 0 or 1; b is 0 or 1; R''' is H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R'''' and R''''' are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6.

20. A pharmaceutical composition in accordance with any one of claims 1 to 9, wherein said compound has the formula:



where: Y is any chemical group; L is a ligand; and R'' is a substituted or unsubstituted divalent hydrocarbon moiety; a is 0 or 1; R''' is H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R'''' and R''''' are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6.

21. A pharmaceutical composition in accordance with claim 20, wherein Y is selected from the group consisting of:  $(\text{R}')_b\text{AuL}'$  and;



where: L' is a ligand; R' is a substituted or unsubstituted divalent hydrocarbon moiety; b is 0 or 1; R''' is H,  $\text{SO}_3^-$ ,  $\text{PO}_4^{2-}$ ,  $\text{CO}_2\text{H}$ , OH,  $(\text{CH}_2)_n\text{CH}_3$ ,  $\text{O}(\text{CH}_2)_n\text{CH}_3$ ,  $\text{S}(\text{CH}_2)_n\text{CH}_3$ , or  $\text{NR}''''\text{C}(\text{O})(\text{R}''''')$  where R'''' and R''''' are  $(\text{CH}_2)_n\text{CH}_3$ ; and n is 0 to 6.

22. A pharmaceutical composition in accordance with any one of claims 14 to 21, wherein L and L' are independently selected from the group consisting of  $\text{PR}_3$ ,  $\text{P}(\text{OR})_3$ ,  $\text{CNR}$ ,  $\text{NCR}$ ,  $\text{PR}_n(\text{CH}_2\text{OR}^\ddagger)_{3-n}$ ,  $\text{N}_4\text{C}_6\text{H}_{12}$ ,  $[\text{N}_4\text{C}_6\text{H}_{12}-\text{N}-\text{CH}_3]^+$ ,  $\text{PN}_3\text{C}_6\text{H}_{12}$ , and  $\text{P}[\text{N}_3\text{C}_6\text{H}_{12}-\text{N}-\text{CH}_3]^+$ , where R is a substituted or unsubstituted hydrocarbon moiety and  $\text{R}^\ddagger$  is selected from the group consisting of H, Me,  $\text{SO}_2^-$ ,  $\text{PO}_3^-$ , alkyl and aryl, and each  $\text{R}^\ddagger$  in any one ligand is the same or different.

23. A pharmaceutical composition in accordance with claim 22, wherein R is a substituted or unsubstituted alkyl, alkene, alkyne, aryl or aromatic group and each R in any one ligand is the same or different.

24. A pharmaceutical composition in accordance with claim 22 or 23, wherein R is selected from the group consisting of methyl, ethyl, propyl, butyl and phenyl groups.
25. A pharmaceutical composition in accordance with claim 22, 23 or 24, wherein the ligand is  $\text{PPh}_3$ .
26. A pharmaceutical composition in accordance with any one of claims 14 to 25, wherein R' and R" are each independently selected from the group consisting of methylene, ethylene, propylene, butylene and phenylene groups.
27. A compound having a gold (I) atom covalently bonded to a carbon atom for use as a chemotherapeutic agent.
28. Use of a compound having a gold (I) atom covalently bonded to a carbon atom in the preparation of a medicament for the treatment of cancer.
29. Use of a compound in accordance with claim 28, wherein the cancer is resistant to a platinum drug.
30. Use of a compound in accordance with claim 29, wherein the cancer is resistant to cisplatinum and/or carboplatinum.
31. Use of a compound in accordance with claim 28, 29 or 30, wherein the cancer is ovarian or lung cancer.
32. Use of a compound in accordance with any one of claims 28 to 31, wherein said compound is defined in accordance with any one of claims 1 to 26.
33. A method of treating a cancer in a human or animal patient comprising administering to said patient a therapeutically effective amount of a compound having a gold (I) atom covalently bonded to a carbon atom.
34. A method in accordance with claim 33, wherein the cancer is resistant to a platinum drug.

35. A method in accordance with claim 34, wherein the cancer is resistant to cisplatinum and/or carboplatinum.
36. A method in accordance with claim 33, 34 or 35, wherein the cancer is ovarian or lung cancer.
37. A method in accordance with any one of claims 33 to 36, wherein said compound is defined in accordance with any one of claims 1 to 26.

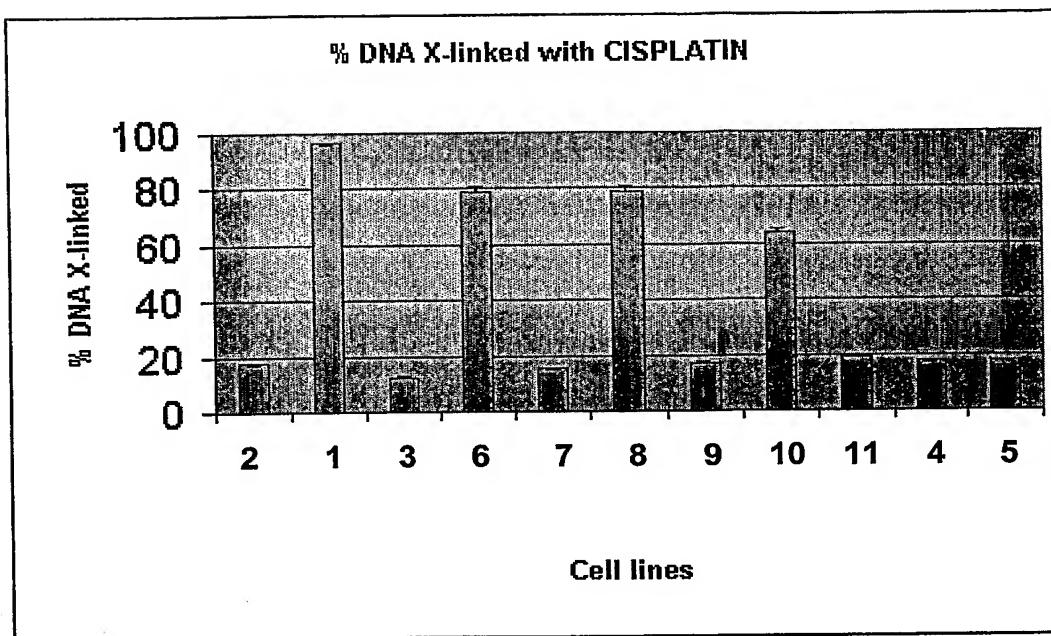


Figure 1. DNA cross-linking in parental and resistant cell lines following treatment with cisplatinum.



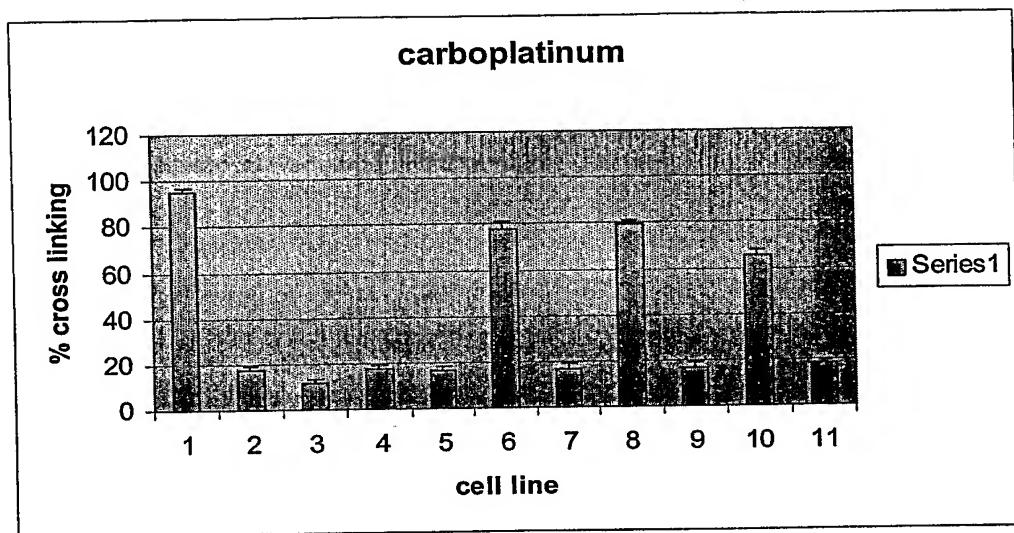


Figure 2. DNA cross-linking in parental and resistant cell lines following treatment with carboplatin.



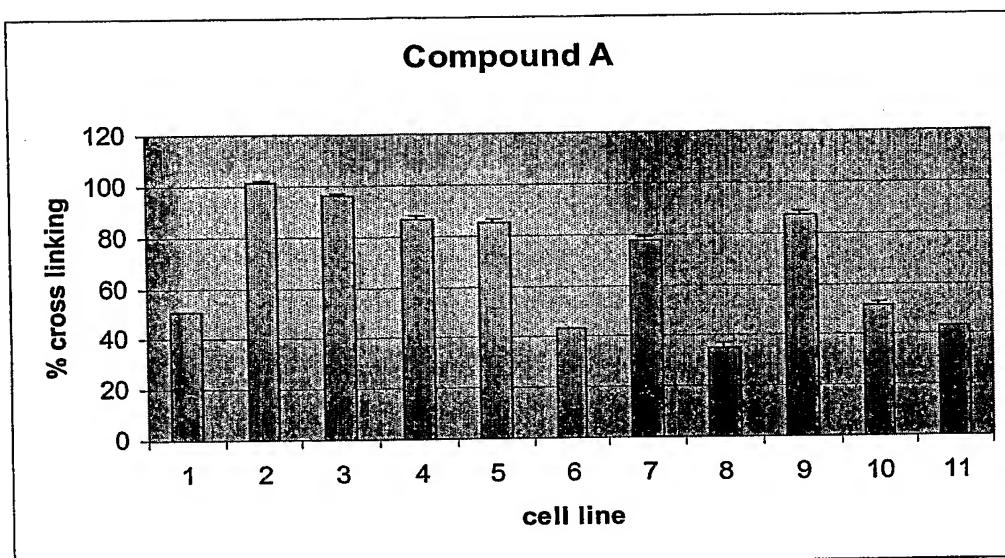


Figure 3. DNA cross-linking in parental and resistant cell lines following treatment with compound A.



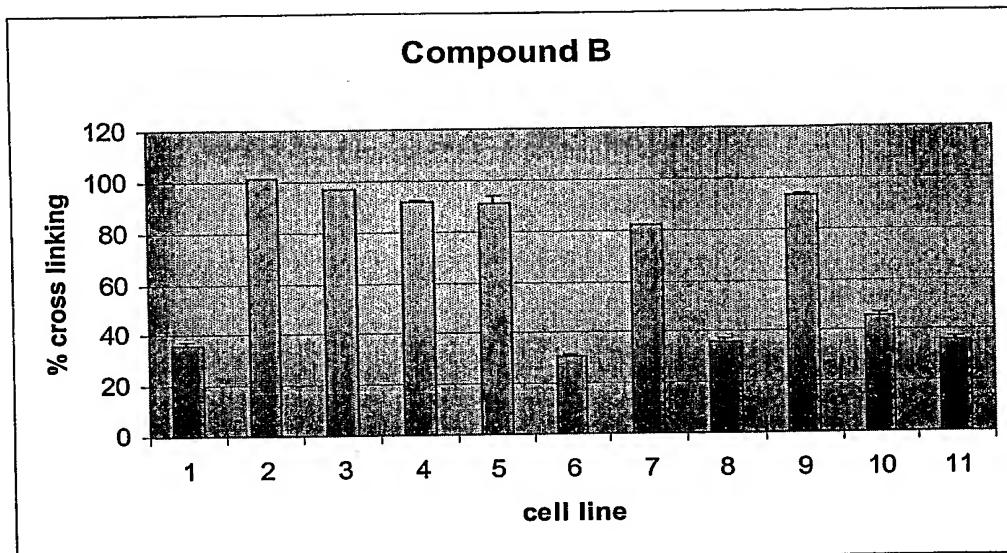


Figure 4. DNA cross-linking in parental and resistant cell lines following treatment with compound B.



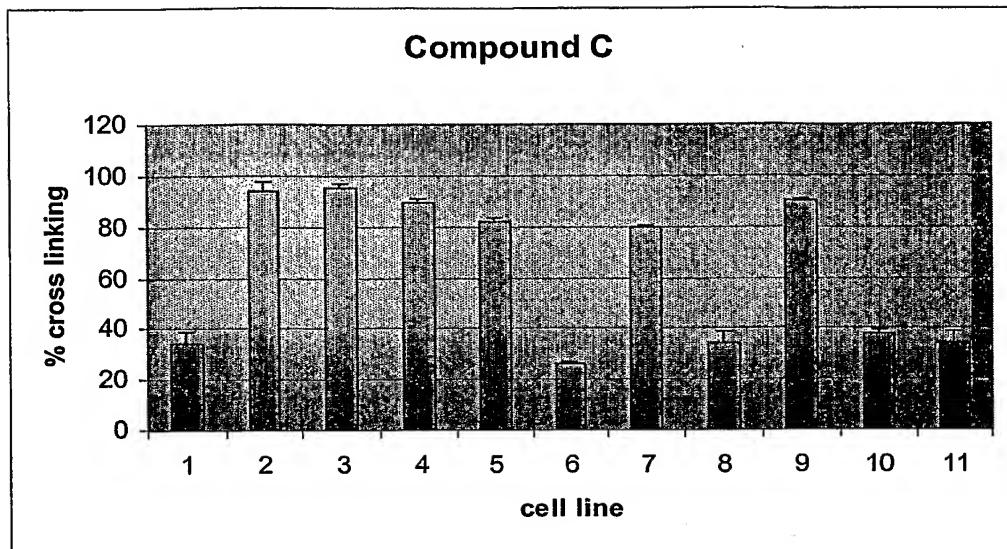


Figure 5. DNA cross-linking in parental and resistant cell lines following treatment with compound C.



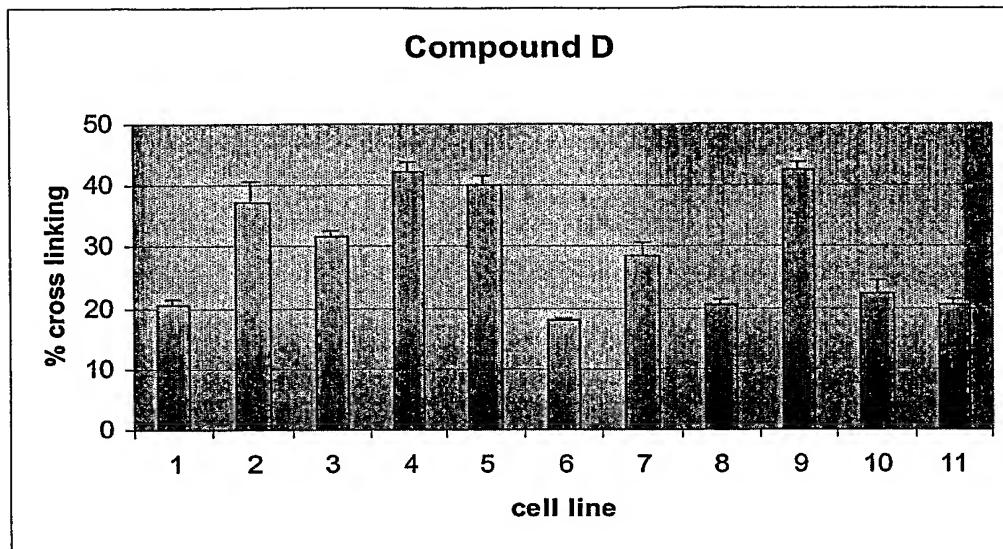


Figure 6. DNA cross-linking in parental and resistant cell lines following treatment with compound D.



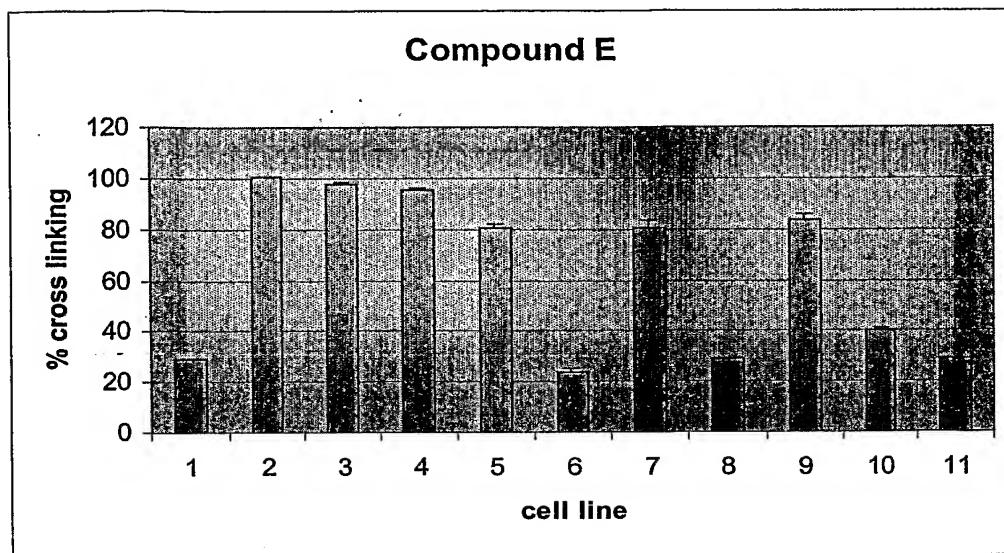
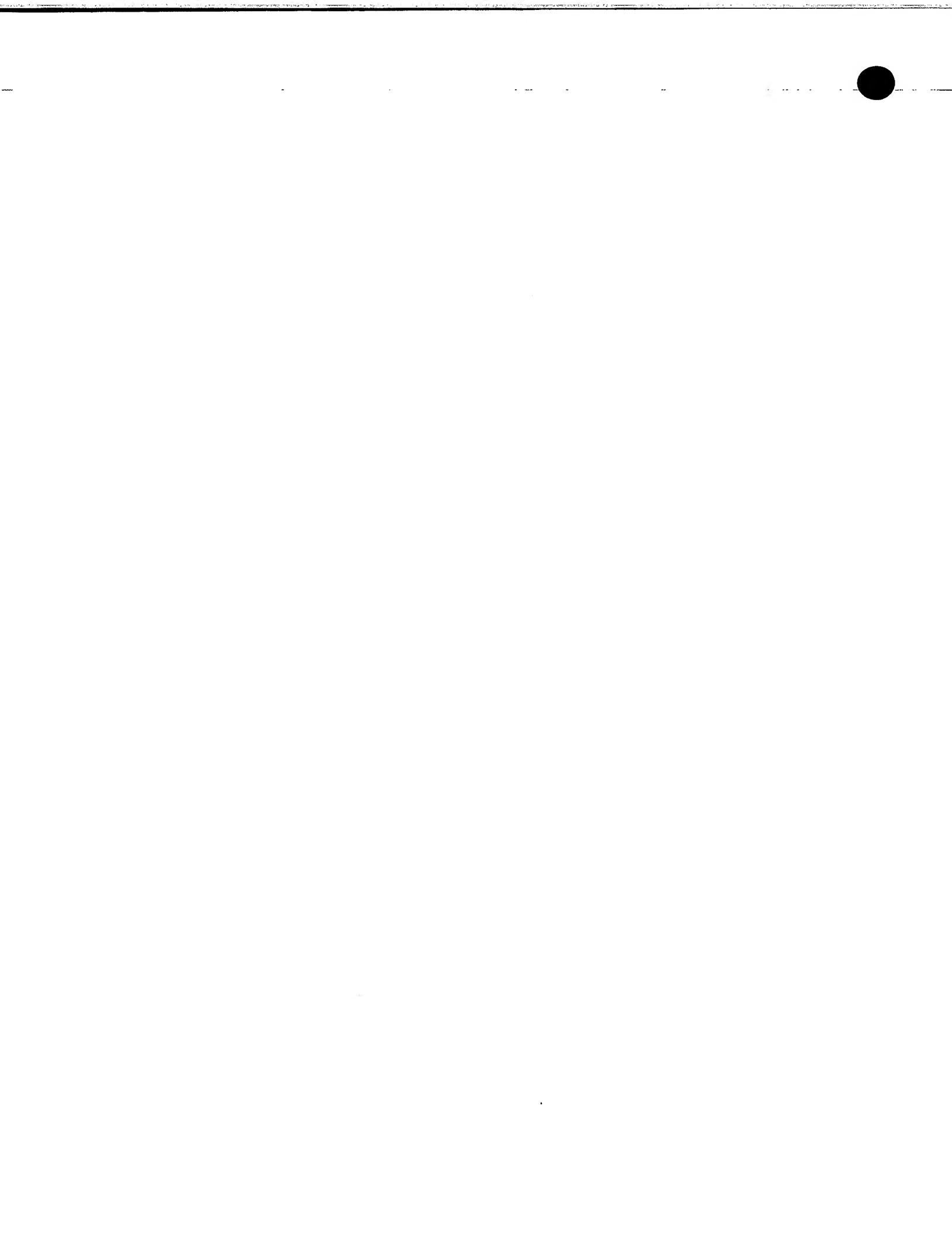


Figure 7. DNA cross-linking in parental and resistant cell lines following treatment with compound E.



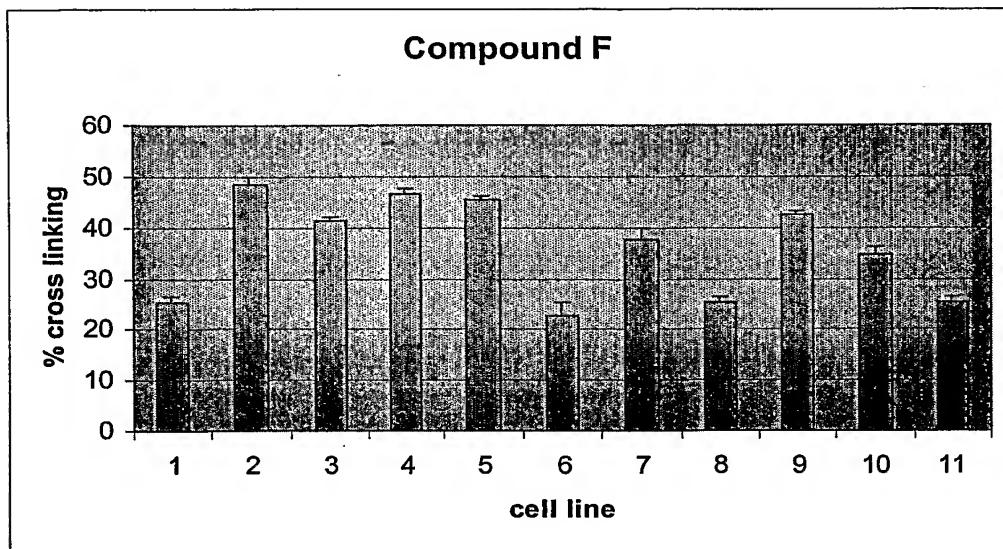


Figure 8. DNA cross-linking in parental and resistant cell lines following treatment with compound F.

